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STEPTOE & JOHNSON LLP 1330 CONNECTICUT AVENUE, N.W. WASHINGTON, DC 20036			EXAMINER CROW, ROBERT THOMAS	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



### **SUPPLEMENTAL ACTION**

1. This Office Action is being provided to correct the number of the U.S. Patent to Monforte et al used in the Office Action mailed 20 February 2008.

The Final Office Action mailed 8 May 2007 relied upon Monforte et al (U.S. Patent No. 5,700,642, issued 23 December 2007). The previous Office Action mailed 20 February 2008 incorrectly listed the number of a different U.S. Patent to Monforte et al as U.S. Patent No. 5,830,642. The correct number of the newly cited prior art of Monforte et al is U.S. Patent No 5,830,655, issued 3 November 1998.

2. The correct number has been provided at all listings within the text. In addition, the typographical error "ad applied to" has been changed to "as applied to)" in the beginning of Sections 11 and 12 below, and the numbers of the Sections have been changed relative to the previous Office Action.

3. It is noted that the correct reference of Monforte et al was provided on the Notice of References Cited mailed 20 February 2008.

4. The remaining text of this Office Action is unchanged.

### ***Continued Examination Under 37 CFR 1.114***

5. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9 November 2007 has been entered.

### ***Status of the Claims***

6. This action is in response to papers filed 9 November 2007 in which claims 1, 7, 22, and 25 were amended, claims 88-89 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

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The objections to the claims listed in the previous Office Action withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments. However, as noted in the Advisory Action mailed 25 October 2007, Applicant admits that a cleavage solution in contact for a hybridized array, if only for "the first instant" and wherein "fewer than all selectively cleavable bonds will be cleaved" meets the limitations of the instant claims.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 1-25, 52-58, and 62-86 are under prosecution.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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9. It is noted that the rejections presented below rely on a prior art patent to Montforte et al that is different from the Montforte patent relied upon in the previous Office Actions.

10. Claims 1-13, 15, 52-58, 62-74, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000).

Regarding claim 1, Monforte et al teach a probe array for qualitative and/or quantitative detection of target molecules in a sample. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (column 38, lines 40-55 and column 15, lines 15-25). The probe molecules have at least one label because the primers are labeled (column 15, lines 35-47), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array (column 15, lines 35-47).

Monforte et al further teach Figure 16, which shows target molecule 133 hybridized to immobilized to first probe molecule bearing cleavage site 127 bound to a target (column 18, lines 25-67). Monforte et al also teach that cleavage step 139 occurs before denaturation (column 18, lines 40-50); thus, before denaturation but after cleavage, the two separate fragments at the bottom of Figure 16 are cleaved but still annealed to one another, and comprising the first target region bound to first cleavage product (i.e., the fragment release from array surface 145; column 18, lines 45-50) and comprising the label (column 15, lines 35-47), and the second target region which is bound to the second region of the probe which is still immobilized to array surface 145. Because denaturation has not yet occurred, the products are still in contact with the cleavage solution.

It is noted that the claim does not require the target to be uncleaved, nor does a review of the specification yield any limiting definition where the two regions of the target molecule are required to

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remain connected. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding “regions” and “targets” (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]))

While Monforte et al teach formulation of an array of the immobilized, cleavable primers. (column 38, lines 40-55 and column 15, lines 15-25), teach the probes of Figure 16 are immobilized to the array surface at any stage (column 18, lines 45-50), and further teach the use of probes for multiplexing (column 41, lines 20-50), which requires a plurality of different probes, Monforte et al do not explicitly teach two different probes on the array surface.

However, Koster et al teach a probe array comprising different sequences at different defined locations (Figure 3) in an ordered array (Figure 5). Koster et al also teach wherein the multiplexing, which requires a plurality of different probes, has the added advantage of allowing multiple simultaneous detection of targets and parallel processing (column 4, lines 13-25). Thus, Koster et al teach the known technique of having multiple different sequences in an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the array comprising immobilized primers for multiplexing as taught by Monforte et al to have multiple different sequences in the array to arrive at the instantly claimed array as taught by Koster et al with a reasonable expectation of success. Because the array has multiple different sequences, not all of the immobilized sequences would bind a single target. Thus, after cleavage, at least one of the immobilized probes that did not bind to the target would be cleaved (i.e., the cleavage product of the second probe of the instant claim), and would be in contact with the cleavage solution before the denaturation step of Monforte et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an array having the added advantage of allowing multiple simultaneous detection of targets and parallel processing as explicitly taught by Koster et al (column 4, lines 13-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the multiple different sequences of

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Koster et al could have been applied to the array of Monforte et al with predictable results because the multiple different sequences of Koster et al predictably result in an array useful for the detection of nucleic acid targets.

Regarding claims 2 and 3, the array of claim 1 is discussed above. Monforte et al teach the first and second probes are oligonucleotides; namely, the probes are oligonucleotide primers (column 4, lines 22-40).

Regarding claim 4, the array of claim 3 is discussed above. Monforte et al also teach the oligonucleotides have a length of from 10 to 100 bases; namely, thirty nucleotides (column 15, lines 35-50).

Regarding claim 5, the array of claim 1 is discussed above. Monforte et al further teach the first cleavage product of the first probe molecule and the second cleavage product of the first probe molecule are approximately the same size; namely, Figure 16, wherein the cleavable linker is between the ends of the primer. The broadly claimed limitation “approximately equal in size” is interpreted to mean the cleavable linkage is in between the two ends due to the lack of explicit structural limitations on the number of bases or nucleotides in either cleavage product.

Regarding claim 6, the array of claim 1 is discussed above. Monforte et al teach the cleavage products are products of non-enzymatic cleavage; namely, the cleavable link is chemically cleavable (column 19, lines 54-67).

Regarding claim 7, the array of claim 1 is discussed above. Monforte et al also teach the cleavage products are products of chemical methods (column 19, lines 54-67).

Regarding claims 8 and 9, the array of claim 1 is discussed above. Monforte et al further teach the cleavage products are products of cleavage by the metal ions; namely, mercury ions (column 22, lines 45-50).

Regarding claim 10, the array of claim 1 is discussed above. Monforte et al teach the cleavage products are products of cleavage by photolysis (column 20, lines 1-5).

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Regarding claims 11-13, the array of claim 1 is discussed above. Monforte et al also teach the cleavage products are products of cleavage of a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid analogs; namely, the cleavable linker is a phosphorothioate within a nucleoside dimer (Figure 1I and column 19, lines 54-67).

Regarding claim 15, the array of claim 1 is discussed above. Monforte et al further teach the label is a detectable label and is fluorescent (column 15, lines 35-50). Fluorescent labels are detectable by labeled reporter probes because signal generating antibodies to the fluorescent labels can be obtained.

Regarding claim 52, the probe array of claim 1 is discussed above. Monforte et al also teach reagents for the selective cleavage of the selectively cleavable bond in the probe molecules in the form of mercuric chloride (column 22, lines 45-50), a hybridization buffer in the form of an annealing buffer (column 27, lines 17-30), and a washing buffer (column 27, lines 40-43).

It is noted that the preamble of this claim recites a "kit." The specification, however, does not define this term, and so it is being interpreted to encompass any collection of reagents that includes all of the elements of the claims. Any further interpretation of the word is considered an "intended use" and does not impart any further structural limitation of on the claimed subject matter. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "kit."

Regarding claims 53-54, the kit of claim 52 is discussed above. Monforte also teach heavy metal ions; namely, mercuric chloride (column 22, lines 45-50).

Regarding claim 55, the kit of claim 52 is discussed above. Monforte et al further teach a reaction chamber; namely, a Petri dish (Example 2).

Regarding claim 56, the kit of claim 52 is discussed above. Monforte et al teach a detection device; namely, a dual microchannel plate detector (Example 4).



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Regarding claim 57, the kit of claim 52 is discussed above. Monforte et al also teach a temperature control unit; namely, a thermocycler (column 35, line 32).

Regarding claim 58, the kit of claim 52 is discussed above. Monforte et al further teach the probe array is in the form of a highly integrated autonomous unit; namely, the array is synthesized on a support in the form of a matrix (column 38, lines 40-55) and the solid support is a slide (Example 2); therefore, the array is integrated because the probes are attached to the slide, and autonomous because the slide exists independently.

Regarding claim 62, Monforte et al teach a probe array. In a single exemplary embodiment, Monforte et al teach an array surface in the form of a solid support having oligonucleotide primers attached at defined sites; namely, in an array (column 38, lines 40-55 and column 15, lines 15-25). The probe molecules have at least one label because the primers are labeled (column 15, lines 35-47), and the probes further have at least one selectively cleavable bond between the site of their immobilization on the array surface and the label; namely, the label is in a fragment of the primer that is releasable from the array (column 15, lines 35-47).

Monforte et al further teach Figure 16, which shows target molecule 133 hybridized to immobilized to first probe molecule bearing cleavage site 127 bound to a target (column 18, lines 25-67). Monforte et al also teach that cleavage step 139 occurs before denaturation (column 18, lines 40-50); thus, before denaturation but after cleavage, the two separate fragments at the bottom of Figure 16 are cleaved but still annealed to one another, and comprising the first target region bound to first cleavage product (i.e., the fragment release from array surface 145; column 18, lines 45-50) and comprising the label (column 15, lines 35-47), and the second target region which is bound to the second region of the probe which is still immobilized to array surface 145. Because denaturation has not yet occurred, the products are still in contact with the cleavage solution.

It is noted that the claim does not require the target to be uncleaved, nor does a review of the specification yield any limiting definition where the two regions of the target molecule are required to

remain connected. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "regions" and "targets."

While Monforte et al teach formulation of an array of the immobilized, cleavable primers. (column 38, lines 40-55 and column 15, lines 15-25), teach the probes of Figure 16 are immobilized to the array surface at any stage (column 18, lines 45-50), and further teach the use of probes for multiplexing (column 41, lines 20-50), which requires a plurality of different probes, Monforte et al do not explicitly teach two different probes on the array surface.

However, Koster et al teach a probe array comprising different sequences at different defined locations (Figure 3) in an ordered array (Figure 5). Koster et al also teach wherein the multiplexing, which requires a plurality of different probes, has the added advantage of allowing multiple simultaneous detection of targets and parallel processing (column 4, lines 13-25). Thus, Koster et al teach the known technique of having multiple different sequences in an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the array comprising immobilized primers for multiplexing as taught by Monforte et al to have multiple different sequences in the array to arrive at the instantly claimed array as taught by Koster et al with a reasonable expectation of success. Because the array has multiple different sequences, not all of the immobilized sequences would bind a single target. Thus, when the solution is added but before cleavage has commenced, at least one probe is bound to the target, at least a second probe is not bound to a target, and both probes still have labels thereon because cleavage has yet to commence. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in an array having the added advantage of allowing multiple simultaneous detection of targets and parallel processing as explicitly taught by Koster et al (column 4, lines 13-25). In addition, it would have been obvious to the ordinary artisan that the known technique of using the multiple different sequences of Koster et al could have been applied to the

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array of Monforte et al with predictable results because the multiple different sequences of Koster et al predictably result in an array useful for the detection of nucleic acid targets.

Regarding claims 63 and 64, the array of claim 62 is discussed above. Monforte et al teach the first and second probes are oligonucleotides; namely, the probes are oligonucleotide primers (column 4, lines 22-40).

Regarding claim 65, the array of claim 64 is discussed above. Monforte et al also teach the oligonucleotides have a length of from 10 to 100 bases; namely, thirty nucleotides (column 15, lines 35-50).

Regarding claim 66, the array of claim 62 is discussed above. Monforte et al further teach the first cleavage product of the first probe molecule and the second cleavage product of the first probe molecule are approximately the same size; namely, Figure 16, wherein the cleavable linker is between the ends of the primer. The broadly claimed limitation "approximately equal in size" is interpreted to mean the cleavable linkage is in between the two ends due to the lack of explicit structural limitations on the number of bases or nucleotides in either cleavage product.

Regarding claim 67, the array of claim 62 is discussed above. Monforte et al teach the selectively cleavable bond cannot be selectively cleaved by enzymatic methods; namely, the cleavable link is chemically cleavable (column 19, lines 54-67), but not enzymatically cleavable.

Regarding claim 68, the array of claim 62 is discussed above. Monforte et al also teach the selectively cleavable bond can be cleaved by chemical methods (column 19, lines 54-67).

Regarding claims 69 and 70, the array of claim 62 is discussed above. Monforte et al further teach the selectively cleavable bond can be selectively cleaved by the mercury ions (column 22, lines 45-50).

Regarding claim 71, the array of claim 62 is discussed above. Monforte et al teach the selectively cleavable bond can be cleaved by photolysis (column 20, lines 1-5).

Regarding claims 72-74, the array of claim 62 is discussed above. Monforte et al also teach the probe molecules comprise a nucleic acid of the formula A1-S-A2, wherein S is a nucleic acid that comprises the at least one selectively cleavable bond and A1 and A2 are any nucleic acids of nucleic acid

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analog; namely, the cleavable linker is a phosphorothioate within a nucleoside dimer (Figure 1I and column 19, lines 54-67).

Regarding claim 76, the array of claim 62 is discussed above. Monforte et al also teach the label is a detectable label and is fluorescent (column 15, lines 35-50). Fluorescent labels are detectable by labeled reporter probes because signal generating antibodies to the fluorescent labels can be obtained.

11. Claims 14 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claims 1 and 62 above, and further in view of Nikiforov et al (U.S. Patent No. 5,518,900, issued 21 May 1996).

Regarding claims 16 and 77, the array of claims 1, 15, 62, and 76 is discussed above in Section 10.

While Monforte et al teach a number of thiolated nucleotides (Figures 1H, 1I, and 1P), neither Monforte et al nor Koster et al teach the functionally equivalent phosphothioate linker.

However, Nikiforov et al teach the preferred use of the functionally equivalent phosphothioate bond in oligonucleotides, wherein the bonds have the added advantage of being exonuclease resistant (column 10, lines 25-50), which results in additional stability towards cellular extracts that may contain exonucleases. Thus, Nikiforov et al teach the known technique of using the functionally equivalent phosphothioate bond in oligonucleotides.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array comprising cleavable linkers of Monforte et al in view of Koster et al with the functionally equivalent cleavable phosphothioate bond to arrive at the instantly claimed invention as taught by Nikiforov et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array having the added advantage of having probes with additional stability towards cellular extracts that may contain exonucleases as a result of the functionally equivalent

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phosphothioate bonds being exonuclease resistant as explicitly taught by Nikiforov et al (column 2, lines 40-63 and Example VI). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent cleavable phosphothioate bond of Nikiforov et al could have been used for the cleavable bond of the array of Monforte et al in view of Koster et al with predictable results because the functionally equivalent cleavable phosphothioate bond of Nikiforov et al predictably results in functionally equivalent cleavable bond.

12. Claims 16 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claims 1, 15, 62, and 76 above, and further in view of Fung et al (U.S. Patent No. 4,757,141, issued 12 July 1988).

Regarding claims 16 and 77, the array of claims 1, 15, 62, and 76 is discussed above in Section 10.

Neither Monforte et al nor Koster et al teach anchor groups.

However, Fung et al teach the attachment of fluorescent labels (i.e., dyes) to probe molecules (i.e., oligonucleotides) using anchor groups (i.e., linkers; Abstract) with the added advantage that the linkers attach the label using automated methods in high yield (i.e., 95%; column 2, lines 40-63 and Example VI). Thus, Fung et al teach the known technique of using anchor groups to attach fluorescent labels to oligonucleotides.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array comprising labels of Monforte et al in view of Koster et al with the anchor groups (i.e., linkers) to arrive at the instantly claimed invention as taught by Fung et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would result in a probe array that is readily labeled using automated method in high yield as explicitly taught by Fung et al (column 2, lines 40-63 and Example VI). In addition, it would have been obvious to the ordinary artisan that the known technique of using the

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anchor of Fung et al could have been used to attach the fluorescent labels of Monforte et al in view of Koster et al with predictable results because the anchor of Fung et al predictably results in reliable method of attaching a label on an oligonucleotide.

13. Claims 17-18, 22-25, 78-79, and 83-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claims 1 and 62 above, and further in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000).

Regarding claims 17-18 and 78-79, the array of claims 1 and 62 is discussed above in Section 10.

Neither Monforte et al nor Koster et al teach third probe molecules (i.e., claims 17 and 78) or random sequences (i.e., claims 18 and 79).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising a first probe molecule in the form of an oligonucleotide that hybridizes to a target (Abstract) and third (i.e., additional) probe molecules that have no selectively cleavable bond (i.e., claims 17 and 78); namely, mismatch control probes, wherein the mismatch control probe is an immobilized oligonucleotide (i.e., an ordinary, non-cleavable oligonucleotide; column 3, lines 30-40). The mismatch probes correspond to oligonucleotide probes (column 3, lines 30-40), which have defined sequences because the mismatch probes have deliberately selected sequences (i.e., claims 18 and 79; column 7, lines 20-22). Lockhart et al also teach the third probes have the added advantage that the third probe molecule (i.e., the mismatch probe) allows measurement of the concentration of hybridized material (column 17, lines 23-27). Thus, Lockhart et al teach the known technique of providing a third probe on the array (i.e., claims 17 and 78) that has a defined sequence (i.e., claims 18 and 79).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to have modified the array comprising immobilized probes of Monforte et al in view of Koster et al with the additional third probe (i.e., claims 17 and 78) having a defined sequence

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(i.e., claims 18 and 79) as taught by Lockhart et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing measurement of the concentration of hybridized material as explicitly taught by Lockhart et al (column 17, lines 23-27). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the third defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the third defined sequence probe of Lockhart et al predictably results in a probe useful for binding assays on arrays.

Regarding claims 22-23 and 83-84, the array of claims 1 and 62 is discussed above. While claim 22 is drawn to fourth probe molecules, the claim does not require third probe molecules. The instantly claimed fourth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claims 1 and 62.

While Monforte et al teach labeled probes having cleavable linkers (column 9, lines 5-10), neither Monforte et al nor Koster et al teach silent a fourth probe molecule which does not have affinity for targets (i.e., claims 22 and 83) that has a defined sequence (i.e., claims 23 and 84). Thus, Lockhart et al teach the known technique of providing a fourth probe on the array (i.e., claims 22 and 83) that has a defined sequence (i.e., claims 23 and 84).

However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target; Abstract) and fourth (i.e., additional) probe molecules having no specific affinity to target molecules; namely, expression level control probes, which are arranged on at least one array element because the probes are on the array (i.e., claims 22 and 83; column 3, lines 50-55). The fourth (i.e. additional) probes have a defined sequence because the expression control probes are complementary to known genes (i.e., claims 23 and 84; column 16, lines 55-61), and have the added advantage that the fourth probes allows measurement of the overall health and metabolic activity of a cell, which allows a

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user to identify whether or not the results of a hybridization assay are due to a change in the amount of a target as a result of a change in the gene being studied or if the results are due to the general state of health of the cells from which the sample was isolated (column 16, lines 34-54).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al with the additional fourth probes (i.e., claims 22 and 83) having a defined sequence (i.e., claims 23 and 84) to arrive at the instantly claimed invention as taught by Lockhart et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of having a control for the overall health and metabolic activity of a cell, which aids in the interpretation of assay results, as explicitly taught by Lockhart et al (column 16, lines 34-54). In addition, it would have been obvious to the ordinary artisan that the known technique of providing the fourth defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the fourth defined sequence probe of Lockhart et al predictably results in a probe useful for binding assays on arrays.

Regarding claims 24-25 and 85-86, the array of claim 1 is discussed above. While claim 24 is drawn to fifth probe molecules, the claim does not require fourth or third probe molecules. The instantly claimed fifth probe molecules are therefore interpreted as a set of probes in addition to the probe molecules of claims 1 and 62.

While Monforte et al teach probe molecules have at least one label (column 9, lines 5-10), at least one selectively cleavable bond between the site of their immobilization on the array surface and the label (i.e., the label is in a fragment of the probe that is releasable from the array; column 9, lines 5-10), Monforte et al are silent with respect to fifth probe molecules which have affinity for spiking molecules (i.e., claims 24 and 85) or array elements distributed over the entire surface of the array on which said fifth probe molecules are located (i.e., claims 25 and 86).



However, Lockhart et al teach immobilized nucleic acids in the form of a high density array of oligonucleotides (Abstract) comprising first probe molecules in the form of an oligonucleotide that hybridizes to a target (Abstract) and fifth (i.e., additional) probe molecules having no specific affinity to target molecules in the form of normalization controls (column 3, lines 50-55) arranged on at least one array element (e.g., on any position on the array; column 16, lines 36-31). The fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample; namely, the normalization controls hybridized to reference oligonucleotides added to the sample (i.e., claims 24 and 85; column 16, lines 1-4). Lockhart et al also teach array elements distributed over the entire surface of the array on which said fifth probe molecules are located; namely, the normalization probes are at multiple positions throughout the array (column 16, lines 26-31). Lockhart et al also teach the fifth probe molecules have a specific affinity to spiking target molecules which are externally added to the sample in sufficient concentration to lead to a clearly detectable signal because the normalization controls hybridized to reference oligonucleotides added to the sample so that a signal is obtained (i.e., claims 25 and 86; column 16, lines 1-4). The fifth probes also have the added advantage that the fifth probe molecule provides a control for variation in signals between arrays (column 16, lines 1-9). Thus, Lockhart et al teach the known technique of providing a fifth probe on the array (i.e., claims 24 and 85) and a specific affinity to spiking target molecules which are externally added (i.e., claims 25 and 86).

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al with the additional fifth probes (i.e., claims 24 and 85) having a specific affinity to spiking target molecules which are externally added (i.e., claims 25 and 86) to arrive at the instantly claimed invention as taught by Lockhart et al et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of providing a control for variation in signals between arrays as explicitly taught by Lockhart et al (column 16, lines 1-9). In addition, it would have been obvious to the ordinary artisan that the known

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technique of providing the fifth defined sequence probe of Lockhart et al could have been used on the array of Monforte et al in view of Koster et al with predictable results because the fifth defined sequence probe of Lockhart et al predictably results in a probe useful for binding assays on arrays.

14. Claims 19 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) as applied to claims 1 and 62 above, and further in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989).

Regarding claims 19 and 80, the array of claims 1 and 62 is discussed above in Section 10.

Neither Monforte et al nor Koster et al teach detectable units that are not linked to probe molecules.

However, Mackay et al teach arrays of polynucleotides in the form of 2-D gels (column 6, lines 56-67) having detectable units that are not attached to probe molecules; namely, calibration chemicals (column 6, lines 56-67), which have the added advantage of acting as calibration standards (column 6, lines 56-67). Thus, Mackay et al teach the known technique of providing arrays having detectable units not linked to probe molecules.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al with the detectable labels not attached to probes (i.e., calibration chemicals) to arrive at the instantly claimed invention as taught by Mackay et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having standardized calibration as explicitly taught by Mackay et al (column 6, lines 56-67). In addition, it would have been obvious to the ordinary artisan that the known technique of providing probe independent detectable labels of Mackay et al could have been used on the array of Monforte et al

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in view of Koster et al with predictable results because the probe independent detectable labels of Mackay et al predictably result in a labels useful for calibrating arrays.

15. Claims 20 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Lockhart et al (U.S Patent No. 6,040,138, issued 21 March 2000) as applied to claims 17 and 78 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claims 20 and 81, the array of claims 17 and 78 is discussed above in Section 13.

Neither Monforte et al Koster et al, nor Lockhart et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al and Lockhart et al with the different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition,

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it would have been obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Monforte et al in view of Koster et al and Lockhart et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

16. Claims 21 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monforte et al (U.S. Patent No. 5,830,655, issued 3 November 1998) in view of Koster et al (U.S. Patent No. 6,043,031, issued 28 March 2000) in view of Mackay et al (U.S. Patent No. 4,874,492, issued 17 October 1989) as applied to claims 19 and 80 above, and further in view of Kievits et al (U.S. Patent No. 5,770,360, issued 23 June 1998).

Regarding claims 21 and 82, the array of claims 19 and 80 is discussed above in Section 15.

Neither Monforte et al, Koster et al, nor Mackay et al teach different degrees in labeling.

However, Kievits et al teach immobilized oligonucleotides comprising a plurality of different probes, wherein the additional (i.e., second) probe molecules are arranged on different array elements; namely, two different oligonucleotide probes are arranged in two different spots (column 5, lines 17-50). The probes are labeled differently (column 5, lines 32-37); therefore, the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe. Kievits et al teach the differential labeling has the added advantage of allowing indication of whether a test result is positive or negative (column 5, lines 17-44), thereby excluding false negatives (column 2, lines 1-9). Thus, Kievits et al teach the known technique of differential labeling.

It would therefore have been obvious to a person having ordinary skill in that art at the time the claimed invention was made to modify the array of Monforte et al in view of Koster et al and Mackay et al with the different degree of labeling to arrive at the instantly claimed invention as taught by Kievits et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make

such a modification because the modification would have resulted in a probe array having the added advantage of allowing indication of whether a test result is positive or negative, thereby excluding false negatives, as explicitly taught by Kievits et al (column 2, lines 1-9 and column 5, lines 17-44). In addition, it would have been obvious to the ordinary artisan that the known technique of differential labeling of Kievits et al could have been used on the array of Monforte et al in view of Koster et al and Mackay et al with predictable results because the differential labeling of Kievits et al predictably result in a labels useful for eliminating false negatives on arrays.

#### *Response to Arguments*

17. Applicant's arguments filed 9 November (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant argues on pages 13-14 of the Remarks that claims 62-86 are not indefinite because at the first instant and for some time after contacting with a cleavage solution, at least some of the probe molecules in contact with the cleaving solution will remain uncleaved.

Applicant's arguments are found persuasive, and the rejection is therefore withdrawn. However, it is noted that Applicant admits that a cleavage solution in contact for a hybridized array, if only for "the first instant" and wherein "fewer than all selectively cleavable bonds will be cleaved" as argued on page 14 of the Remarks, meets the limitations of the claims.

B. As noted in the Advisory Action mailed 25 October 2007, the arguments regarding the anticipation of the claims by Koster et al are persuasive, and the rejection is withdrawn.

C. As noted above in Section 5, the rejections presented in this Office Action rely on a prior art patent to Montforte et al that is different from the Montforte patent relied upon in the previous Office Actions. Thus, all arguments regarding the previous rejections using the 5,700,642 patent of Montforte et al have been considered but are moot in view of the new rejections necessitated by the amendments.

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D. All further arguments in the Remarks are considered as they apply to the instant rejections necessitated by the amendments, and reiterate the response to the arguments presented in the Advisory Action mailed 25 October 2007

E. Applicant argues on page 18 of the Remarks that Fung et al do not teach anchor groups in accordance with page 40 of the instant specification.

However, this argument is confusing because paragraph 0091 of the instant specification recites an embodiment wherein a detectable unit is a fluorophore, and an anchor group is a group wherein the detectable unit is coupled. Applicant's citation of page 40 recites an embodiment wherein the anchor group is reacted with specifically binding components, which is a different embodiment of an anchoring group compared to that of paragraph 0091. Fung et al teach anchoring groups in the form of linkers which are attached to fluorescent labels to nucleic acids (Abstract). The linkers of Fung et al are thus "anchors" in accordance with paragraph 0091 of the instant specification, and the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "anchors" (In re Hyatt, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1])).

F. Applicant argues on pages 18-19 of the Remarks that Lockhart et al does not teach labeled probes are immobilized.

As noted in the previous Office Action, Lockhart et al is solely relied upon for the third through fifth probes. Monforte et al already teach labeled immobilized probes as detailed in the rejections above; thus, Monforte et al teach provide a teaching of immobilized labeled probes, and no teaching of immobilization is required by Lockhart et al.

G. Applicant argues on page 21 of the Remarks that Kievits et al do not teach the differing labeling degree of the instant claims.

However, Applicant's citation of the specification for a definition of a different of degree of labeling begins with the phrase "for example with a defined mixture...." The phrase "for example" indicated the recitation is to a single embodiment, and not a limiting definition. Kievits et al teach a

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differing degree of labeling as detailed above and in the previous Office Action. Because Applicant's citation is not a limiting definition, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "differing degree of labeling."

H. Applicant's remaining arguments with respect to the previous rejections of the claims have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

### *Conclusion*

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert T. Crow/  
Examiner, Art Unit 1634

Robert T. Crow  
Examiner  
Art Unit 1634

/Diana B. Johannsen/  
Primary Examiner, Art Unit 1634